Gene Scene

Why should primary care physicians know about the genetics of dementia?

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Patient 1
An 80-year-old woman is accompanied by her son, who reports that she has become progressively confused and unable to manage her own affairs. A thorough evaluation reveals dementia, but no specific cause is identified. Her son mentions apolipoprotein E (*APOE*) testing, a test he has read about on the Internet, and wonders if it might help figure out if his mother has Alzheimer's.

Patient 2
A successful 45-year-old engineer became so disoriented on a recent trip that he could remember neither the name of his hotel nor the city he was visiting. In his physician's office, the findings of an examination were notable only for his memory difficulties: he knew his name but could not recall his address, the name of the US president, or 3 new objects. He noted that "the same thing happened to my mother." He wonders what's wrong and if he somehow caught it from her.

Dementia has multiple genetic and nongenetic causes. In a patient with probable dementia, the initial evaluation should be directed toward detecting treatable causes.[1] In addition to dementia, depression and delirium need to be considered (see box).[2] Alzheimer disease (AD), the most common cause of dementia in North America and Europe, accounts for about half of dementia cases, with most of the rest due to cerebrovascular disease. Some degenerative neurologic conditions, such as Parkinson's disease, present with dementia in combination with other neurologic findings.

AD typically begins with subtle and poorly recognized failure of memory that slowly becomes more severe and, eventually, incapacitating. Other common symptoms include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally seizures, parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism develop.[3,4] Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is 8 to 10 years, with a range of 1 to 25 years. The clinical diagnosis of AD can be supported by neuroimaging studies that show gross cerebral cortical atrophy.[5] Premortem diagnosis is correct 80% to 90% of the time by autopsy confirmation.[6,7]

Summary points

- A test for genetic variants of the apolipoprotein-E protein can identify individuals with an increased or decreased likelihood of late-onset Alzheimer disease
- Although the use of this test has been suggested by some as part of the workup for dementia, it is not sensitive or specific enough to preclude other investigations for dementia
- The same test can be used to identify asymptomatic people with an increased risk of Alzheimer disease, but several expert panels have recommended against such testing
- Some patients develop early-onset familial dementia on a genetic basis, and genetic testing may be helpful in such families

PREVALENCE

The prevalence of dementia increases with increasing age; about 10% of all persons older than 70 years have significant memory loss, and more than half of these individuals have AD. The prevalence of dementia in persons older than 85 years is estimated to be 25% to 45%.

VARIANTS OF AD

AD can be categorized as sporadic, familial (late or early onset), or that associated with Down syndrome (table 1).

Patients with familial and sporadic AD have the same clinical and pathologic phenotypes but differ in the pres-

Courtesy of Alzheimer's Association

Alzheimer disease begins with subtle memory failure that then progresses

Conditions presenting as dementia

Potentially treatable causes

- Depression
- Delirium
- Drug and toxin reaction (eg, alcohol intoxication or withdrawal or use of analgesic, anticholinergic, psychotropic, and sedative-hypnotic medications)
- Thyroid disease
- Vitamin deficiencies (eg, vitamin B_{12} and thiamine)
- Normal-pressure hydrocephalus
- Central nervous system infection (eg, chronic meningitis, tertiary syphilis)
- Neoplasm
- Cerebrovascular disease

Degenerative diseases associated with dementia

- Frontotemporal dementia

  Pick's disease
- Parkinson's disease
- Diffuse Lewy body disease
- Creutzfeldt-Jakob disease
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADSIL)

ence or absence of family history of AD, respectively.[8,9] The onset of sporadic AD can be anytime in adulthood. The pathogenesis is thought to be multifactorial, resulting from a combination of aging, genetic predisposition, and exposure to 1 or more as-yet-unconfirmed environmental agents such as head trauma, viruses, and toxins.[4] A strong family history or molecular genetic testing distinguishes persons with familial AD from those with the sporadic form. Early- and late-onset familial AD are thought to each have different modes of inheritance and implicated genes. In the more common late-onset familial form, the mean age of onset is after 65 years. Less than 5% of families with AD have the early-onset familial form, with onset consistently before age 65.

Table 1 *Prevalence of different causes of Alzheimer disease (AD)*

AD type	Proportion of all cases of AD, %
Sporadic	About 75
Familial	About 25
Late-onset (AD2)	15–25
Early-onset (AD1, AD3, AD4)	<5
Associated with Down syndrome	<1

MOLECULAR GENETIC TESTING

Late-onset familial AD

Late-onset familial AD is a complex disorder that may involve multiple genes that increase an individual's susceptibility; no specific gene has been implicated as causative. The association of apolipoprotein E ε4 (*APOE* ε4) with late-onset AD is well documented, but the usefulness of *APOE* testing in clinical diagnosis and risk assessment remains unclear.[10-12]

Three common variants of *APOE* occur: ε2, ε3, and ε4. Epidemiologic studies have documented *APOE* ε4 as a risk factor for AD (table 2)[13-17] whereas *APOE* ε2 appears to reduce risk. In patients with dementia and suspected AD, the presence of 1 or more *APOE* ε4 alleles has been shown to increase the specificity of the diagnosis in studies of white populations.[18,19] However, the presence of an *APOE* ε4 allele, even a homozygous ε4/ε4 genotype, is not diagnostic for AD and, therefore, does not lessen the need to evaluate other causes of dementia, particularly treatable causes. The absence of *APOE* ε4 does not eliminate the diagnosis of AD. *APOE* genotyping was not found to be of significant diagnostic use in identifying AD in a community-based sample with late-onset dementia.[19] *APOE* ε4 testing in the differential diagnosis of dementia may possibly be of less value in African Americans than in European Americans. One study of *APOE* ε4 status as a predictor of AD risk found no association for African Americans,[15] and another found that the *APOE* ε4 allele is more predictive of familial aggregation of AD among whites than among Hispanics and African Americans, in whom other genetic or nongenetic factors may have a greater influence on the risk for AD in relatives.[20]

Another indication for genetic testing could be to direct therapy. Currently, there is no proven therapy for AD. Management is supportive and individualized to particular symptoms. In many studies, a few patients show modest but useful behavioral or cognitive benefit with therapies that increase cholinergic activity by inhibiting acetylcholinesterase, such as tacrine, and newer, less hepatotoxic

Courtesy of Alzheimer's Association

10% of people over 70 have memory loss, and over half of these have Alzheimer disease

Table 2 *Risk of Alzheimer disease (AD) or dementia according to* APOE *genotype*

Risk assessed	Ethnicity	Odds ratio (95% confidence interval) for 1 or 2 *APOE* ε4 alleles	1 *APOE* ε4 allele	2 *APOE* ε4 alleles
AD before age 65 *and* family history*[13]	White (Netherlands)	3.3 (1.6-7.0)	2.6 (1.2-5.7)	7.9 (1.7-36.0)
AD before age 65 *and* no family history*[13]	White (Netherlands)	1.9 (1.0-3.7)	1.6 (0.8-3.2)	4.9 (1.3-19.9)
AD after age 65[14]	Predominantly white (Boston)	2.3 (1.1-4.9)†		
AD after age 65[15]	White (New York)	2.5 (1.1-6.4)†		
AD after age 65[15]	Black (New York)	1.0 (0.6-1.6)†		
AD after age 65[15]	Hispanic (New York)	1.1 (0.7-1.6)†		
AD in HMO population *and* family history*[16]	White (Seattle)		5.0 (2.0-11.0)‡	12.0 (3.0-59.0)
AD in HMO population *and* no family history*[16]	White (Seattle)		2.3 (1.4-4.0)‡	No controls identified
Dementia after age 85 *and* family history*[17]	White (Oregon)	9.1 (1.7-47.8)		
Dementia after age 85 *and* no family history*[17]	White (Oregon)	4.3 (0.99-1.04)		

HMO = health maintenance organization.
*Family history is defined in table 3.
†*APOE* ε4/*APOE* ε2 was excluded from analysis.
‡*APOE* ε3/*APOE* ε4 only.

drugs with similar pharmacologic action, such as donepezil, rivastigmine, and galantamine.[21-23] The effect of *APOE* status on the response to tacrine has been evaluated in a few small studies with conflicting results.[24-26] To date, there is no scientific basis for determining management on the basis of *APOE* status.

Possible risks of the *APOE* ε4 test

There are potential psychological and economic risks of genetic testing. These possible effects are likely to be of less concern for a patient already diagnosed with dementia than for members of the patient's family confronting their own risk for inheriting the disease susceptibility. Adverse psychological effects include anxiety or stigmatization as a result of knowledge of increased genetic susceptibility. Children of an affected person are at increased risk for AD on the basis of their family history (table 3),[13,16,17] even in the absence of *APOE* testing. If a parent with AD is found to be homozygous for *APOE* ε4, the children, who will thus have at least 1 copy of the *APOE* ε4 allele, have at least a 2 to 3 times higher risk than average of developing AD. They are estimated to have a 61% risk of developing it by age 90[27] (table 4)[28] and a higher risk of developing AD before age 65 (see table 2). Although knowledge of their parent's *APOE* status may indicate increased risk, it does not allow offspring to anticipate with certainty whether they will develop AD and, if so, at what age. Nor is there treatment available to carriers of *APOE* ε4 alleles to prevent the disease.

Economic repercussions include employment or insurance discrimination. For example, an employer's knowledge of a worker's increased risk for AD could conceivably influence employment or promotion decision. Knowledge

Table 3 *Risk of Alzheimer disease (AD) with positive family history*

Risk assessed	Definition of "positive family history"	Odds ratio (95% confidence interval) for positive vs negative family history
AD before age 65 in people with no *APOE* ε4 allele[13]	Reported by subject, confirmed by sibling of ≥1 first-degree relative with dementia	2.9 (1.6-5.6)
AD in HMO population[16]	Reported by subject or surrogate of parent or sibling with progressive memory problems that interfere with daily activities	2.7 (1.8-4.0)
AD after age 85[17]	Reported by subject or surrogate of parent or sibling with AD, dementia, or progressive memory loss	3.8 (0.9-16.5)

HMO = health maintenance organization.

Table 4 *Lifetime risk of Alzheimer disease (AD) in people with a family history of AD according to* APOE *genotype of affected relative**

APOE ε4 genotype of proband	Risk of AD by age 90 in 1st-degree relative, %
APOE ε4/*APOE* ε4	61
APOE ε4/*APOE* ε3	46
APOE ε3/*APOE* ε3	29

*From Martinez et al.[28]

of an increased risk of AD could make it harder for someone to obtain life insurance or individually-rated health insurance. These possibilities underscore the concerns many policymakers have expressed about the importance of preserving the confidentiality of predictive genetic information and preventing insurers and employers from using it.[29,30]

Early-onset familial AD and molecular genetic testing

Early-onset familial AD cannot be clinically distinguished from the sporadic form except on the basis of family history and age of onset. Sixty-one percent of these individuals with early-onset AD had a positive family history; and 13% met stringent criteria for autosomal dominant inheritance (that is, affected individuals in 3 generations).[31] Early-onset dementia does not invariably indicate a genetic cause. If it occurs in the absence of a family history of dementia, our current state of knowledge suggests that the cause is often nongenetic.

Three clinically indistinguishable subtypes of early-onset familial AD have been identified based on the underlying genetic mutations. The most common subtype, AD3, is associated with a mutation in the *PSEN1* gene and occurs in 20% to 70% of patients with early-onset familial AD. Clinically available genetic testing for this gene is used in diagnosis and genetic counseling. Mutations in the *PSEN1* gene have nearly 100% penetrance—that is, almost all people with the gene get early-onset dementia. The age of onset is usually in the 40s or early 50s. Onset after age 65 is thought to be rare, with penetrance essentially complete by that age. However, testing for *PSEN1* is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. (See GeneClinics [www.geneclinics.org] and GeneTests [www.genetests.org] web sites for further information.)

GENETIC COUNSELING

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.[32] Because AD is genetically heterogeneous, genetic counseling of persons with the disease and their family members must be tailored to the information available for that family. AD is common, and the overall lifetime risk of developing dementia is about 10% to 12% in the absence of a family history. Genetic counseling for people with the sporadic type of AD and their family members must be empiric and relatively nonspecific. First-degree relatives of a person with the disease have a cumulative lifetime risk of about 20% to 25% of developing it themselves.[33,34] Presumably, when several individuals in a family have AD, the risk is further increased, as detailed in tables 2 through 4.

Early-onset familial AD is inherited in an autosomal dominant manner in those families with affected members in multiple generations and/or in the case of AD3, documentation of a disease-causing mutation in *PSEN1* gene. In these families, the risk of inheriting the disease-causing *PSEN1* gene is 50% for each child of an affected person. If individuals with early-onset AD are found to have an identifiable mutation in the *PSEN1* gene, testing could be offered to their adult children to determine whether the offspring have inherited the predisposition to early-onset familial AD. This option may or may not be of interest to different family members, and discussion of the implications of testing may be difficult for the family.[35] Patients' primary care providers may play a crucial role in ensuring that family members' needs for information, counseling, and emotional support are addressed over time. Prenatal testing, although clinically available, is unusual for adult-onset disorders.

Patient 1

The physician discussed with the patient and her son that the diagnosis of AD is made clinically with a fair degree of certainty but that the tests currently available (including *APOE* ε4) are not definitive. Recognizing that the son and his siblings were also concerned with the implications to them of the diagnosis of their mother's AD, the physician gave them basic information, then referred them to a genetic counselor. The counselor addressed many of their remaining questions about their own risks of AD and the benefits, risks, and the uncertainty of *APOE* test results, even if positive. The mother was subsequently diagnosed with AD clinically but did not have *APOE* testing.

Patient 2

A careful 3-generation family history taking found that the patient's mother and maternal uncle and

grandfather had debilitating memory problems beginning before age 50. This family history is consistent with autosomal dominant early-onset familial AD. Unlike the questions of the uncertain probability of the son developing dementia in the case discussed above, almost all people who inherit the *PSEN1* gene get early-onset dementia. The family received genetic counseling that included learning about options for genetic testing. After considerable discussion in the family, the patient underwent genetic testing and was found to have an identifiable mutation in the *PSEN1* gene. Testing was offered to his 2 adult children to determine whether they have inherited the predisposition to early-onset familial AD. They are each still contemplating whether to get the testing done.

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